Review Article

PARASITES AND CANCER: A REVIEW OF THE EMERGENCE OF PROTOZOAN CARCINOGENESIS AND NOVEL MOLECULAR INSIGHTS.

Ajetunmobi OI[1], Onyedibe KI[2], Emmanuel I[3]

[1]Department of Histopathology, Federal Medical Centre, Makurdi, Benue State, Nigeria.
[2]Department of Microbiology, Jos University Teaching Hospital, Plateau State, Nigeria.
[3]Department of Histopathology, Jos University Teaching Hospital, Plateau State, Nigeria.

ABSTRACT

The role of infectious agents in the formation of cancers has been long established. However the bulk of the emphasis has been on oncogenic DNA viruses and to a lesser extent, bacteria. However, amidst parasites, only a few metazoans have been linked to cancer, and with feeble molecular bases. This review explores the role of protozoa in cancer formation and highlights new insights into the process of oncogenesis by previously identified helminths with carcinogenic potential. It expounds on the impact of parasites on aspects of cell growth and function, particularly apoptosis, gene expression and cell proliferation.

KEYWORDS: Protozoa, Cancer, Oncogenesis, Helminths, Apoptosis.

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BACKGROUND

Cancer has assumed and maintained a state of public health importance. Unravelling the aetiopathogenesis of common cancers is key to effective control. Microbial infections have become increasingly important in the formation of cancers, and are of greater importance in tropical parts of the world. Most of the emphasis has been on viruses and bacteria, and although largely overlooked, protozoa are an increasingly important factor in microbial carcinogenesis.

The International Agency for Research on Cancer [IARC], in 1990, stated that Schistosoma haematobium infection was associated with a five-fold increase in the risk of squamous cell carcinoma of the bladder, while in 1994, direct links were documented between Liver Flukes [Opistorchis sp and Clonorchis sp] and cholangiocarcinoma of both intra and extra hepatic bile ducts.[1]

Notably Plasmodium falciparum infection has been labelled as a co-factor in the pathogenesis of endemic Burkitt lymphoma.[2] Although several studies suggest an association between malaria and BL, there has never been a conclusive population study in support of a direct role of malaria in causation of BL.[2] Over the last few decades there has been an increased intensity in the search for scientifically viable links between parasites and cancers, especially in the background of "double burden of disease" in tropical regions as well as improved survival of immunosuppressed individuals. Cancers arise from abnormal unregulated growth of cells leading to abnormal form or function of body organs. It has attained a status of global public health importance, accounting for more deaths than HIV and Tuberculosis combined.[3] Cancer has defied previously imposed labels of "disease of rich nations" accounting for an increasing number of deaths in Africa and other 3rd world regions. The cancer burden in developing countries is approaching pandemic proportions.[3] More than half of the 12.4 million new cases of cancer in 2008, and two-thirds of the estimated 7.6 million deaths occur in low and middle income countries.[3] Once shrouded in mystery, there has been an explosion of knowledge with regards the inception and progression of cancers. Consequently, the role of infection has been radically redefined in the last few years, attaining a state of increasing relevance. The American Cancer Society recently stated that infections are linked to 15-20% of cancers, while El-Gayar observed that cancer cases in developing countries can be lowered by more than 25%, if infections are properly treated.[4,5] It is equally estimated that cancers attributable to infections

Corresponding Author: Dr. Innocent Emmanuel
Department of Histopathology,
Jos University Teaching Hospital, Jos.
E-mail: kinapele58@yahoo.com
08065386111

accounted for 17.8% of global cancer burden, while there would be 7.7% less cancer cases in the developed world if associated infections were treated or prevented.[6] Notably, it has been documented that cancers due to infections are progressively increasing.[7]

Infectious agents have been known to incite a chronic inflammatory response with generation of genotoxic free radicals, an altered internal milieu of cytokines stimulating rapid cell turnover and metaplastic change.[8] These create a biological setting predisposing to genetic damage and impaired DNA repair. However, microbial pathogens are now known to directly cause DNA mutations, cell cycle modulation, dysregulation of DNA and resistance to apoptosis. [9] A larger part of the available literature on infection associated cancers has revolved around the role of viruses and bacteria. Insomuch that it has been once stated that "the classic theory of carcinogenesis revolves around radiation, chemicals and viral infection".[10] Helminths, on the other hand, are largely believed to largely cause self limiting infectious ailments, save in states of immunosuppression where the prognosis is worsened by an impaired immune response. Amidst parasites/helminths, only multicellular metazoans such as liver flukes and Schistosomes are presently recognized by the International Agency for Research in Cancer [IARC] to have established roles in carcinogenesis.[1]

The first link between parasites and cancers was first highlighted by Fibiger in 1926.[11]He observed that mice infected with Spiroptera later developed gastric cancer. This was later disproved by other researchers.[11] However, this heightened the interest in the possible role of protozoa in cancers and has led to the unearthing of numerous new concepts about the impact of protozoa in the formation and progression of cancers. Recent research has led to an increase in the number of protozoan pathogens with suspected or confirmed roles as carcinogens. In the same vein, molecular changes that underlie the neoplastic changes seen in a background of known parasitic carcinogens have been unravelled a step further. This article will look at new molecular pathways implicated in parasite induced carcinogenesis, particularly with regards cell cycle regulation, apoptosis, and DNA repair, while exploring links between recently unassociated protozoans and cancers. It equally seeks to strengthen the case for increased surveillance, prophylaxis and treatment of parasitic infection as part of cancer control and prevention.

METHOD OF REVIEW

To review relevant literature on the role of parasites in the formation of cancers, emphasizing largely overlooked protozoa and recently elucidated molecular pathways in both protozoan and metazoan carcinogenesis, we conducted a database search (on Pub Med and Google Scholar) using broad terms related to the intended review such as Parasites and Cancer, Carcinogenic Protozoa, Molecular basis of Parasitic Carcinogenesis. Etc. references in the identified articles were also screened. A total of 79 articles published in English were found, of which 11 were unobtainable. Articles found were screened for content and relevance. Of the 68 articles identified, 65 were found relevant and referenced.

PROTOZOA AND THEIR NOVEL PATHWAYS OF TUMORIGENESIS

Cryptosporidium parvum

This unicellular protozoan is a genus of Apicomplexa and class Sporozoa that causes infections of the gastrointestinal and respiratory tracts.[12] It's a frequent cause of diarrhea in both immunocompetent and immune deficient individuals. Its presence however, carries a higher risk of colorectal malignancy in severe immunosuppression.[13]A study in Poland showed that Cryptosporidium parvum was seen in 18% of cases of colorectal cancer, while a study by El-gayar observed that in mice having cryptosporidiosis, adenomas and invasive neoplasia were detected in the stomach duodenum and ileocecal region.[5,14] A study in Egypt observed dysplastic changes in 80% of colonic biopsies of rats infected with Cryptosporidium parvum , while Certad documented an increase in mitosis, alongside low and high grade intra epithelial neoplasia in different areas of the digestive tract.[14,15]

Increased mitosis was demonstrated on a molecular level in studies by Certad, which show enhanced staining with Ki-67, [a marker of mitosis] while an increased expression of the cell cycle protein, Cyclin D1 was observed in an animal study by Abdou et al.[14,15] Several other studies have documented alterations in the expression of inhibitors of apoptosis such as Bcl2, as well as activation of the pro-mitotic NF-kappab system.[16,17] These various molecular changes drive cellular proliferation. Nonetheless, Cryptosporidium could have pro or anti apoptotic effects depending the stage of its life cycle.[16,17,18] At its trophozoite stage it inhibits apoptosis, while it promotes apoptosis at the sporozoite and merozoite stages.[16]

Toxoplasma gondii

Toxoplasma gondii is a coccidian unicellular protozoan of the class Sporozoa and genus Toxoplasma. The first recorded relationship between this obligate intracellular parasite and neoplasia was in 1967.[5] A positive correlation between the prevalence of Toxoplasma gondii and brain cancer in adults has

been demonstrated in 37 countries, while in France, an increased seroprevalence of Toxoplama gondii has been shown to be associated with increased brain cancer mortality.[9, 19] While elevated levels of anti Toxoplasma gondii antibodies have been seen in cases of meningioma and glioma, El-Gayar also documented increased risks for Hodgkin's and intraocular lymphomas in patients infected with the protozoan. [5, 19,20] In Korea, the incidence of both primary and metastatic brain tumors were observed to be significantly higher in individuals infected with this intracellular protozoan.[21] In addition, the Chinese study by Yuan et al demonstrated an increase in the incidence of Nasopharyngeal and rectal carcinomas in the presence of Toxoplasmosis.[22]

Toxoplasma persists in brain tissue within neurons, macrophages and pseudocysts, thus triggering a chronic inflammatory state. It is also known to alter host cell signaling, motility and morphology.[23] Molecular studies have demonstrated that Toxoplasma turns host cells resistant to apoptosis by impairing activation of pro-apoptotic molecules such as caspase-8, Bax and Bak while promoting the actions of anti-apoptotic agents Bcl2 and Bfl1.[24] It sequesters the inhibitor component of NFkB, thus unleashing its pro-mitotic functions.[23] This protozoan has also been demonstrated to gain control of host cells, and up regulates miR-1792 cluster which is associated with brain cancers.[25] This cluster of micro-RNAs is pivotal to the regulation of the cell-cycle, proliferation and apoptosis.[26] Its dysregulation has been equally strongly linked to haematopoietic and solid cancers, insomuch that it is equally referred to as "oncomir-1".[26] Cells infected with Toxoplasma have been shown to be resistant to Fas-dependent and Fas-independent pathways of Cytotoxic T cell induced apoptosis.[24] Bradyzoites of this organism have been demonstrated to impede apoptosis following exposure to UV and gamma irradiation, toxins and deficiency of growth factors.[27-29] The growth effects of Toxoplasma have been demonstrated to vary, depending on its developmental stage. Latent slow growing bradyzoites induce gene dysregulation to a lesser extent than faster growing tachyzoites.[23]

Trichomonas vaginalis

This protozoan is a pear shaped flagellated organism of the class Mastigophora, and genus Trichomonas is known to cause vaginitis in females and urethritis in males.[12] It has recently been linked to two malignancies of the reproductive tract, cervical cancer in females and prostate cancer in males. In the United states and Canada, the incidence of cervical cancer was said to be three times higher in persons with infection with T.vaginalis while infection with the organism was observed in 4-5% of cervical cancer cases in China.[5, 30] Seropositivity for T.vaginalis was associated with a statistically significant elevation in the risk of metastatic cancer of the prostate.[31,32] African Americans who have the highest risk of carcinoma of the prostate, equally have the highest incidence of trichomoniasis, while the level of serum antibodies against a-actinin protein [derived from T.Vaginalis] correlates with an increased risk of having prostate cancer.[23,31]

Upon adherence and entry into Prostatic Epithelial cells [PECs], this organism triggers proto-oncogenes such as [c-myc, PIM1 and HMGA1], which drive limitless cell proliferation.[5] T.vaginalis has also been demonstrated to alter the expression of junctional proteins such as E-cadherin, Occludin, and ZO-1.[5] A T.vaginalis protein, homologous to Human Macrophage Inhibitory Factor [MIF] has been identified in infected cells.[32] This protein, called TvMIF triggers pathways involved in cell proliferation and inflammation. TvMIF activates the anti-apoptotic Akt pathway via silencing of the pro-apoptotic BAD protein.[32] Its human homologue has been implicated in oncogenic transformation, as over expression has been observed in various human cancers. Interestingly, MIF over expression interferes with p53 activity, thus promoting accumulation of oncogenic mutations.[33]

With regards cervical cancer, a study by Donders observed that T. Vaginalis infection correlated positively with both low risk and high risk HPV infection.[34] Infection with this protozoan was associated with a slightly higher rate of Atypical Squamous Cells of Undetermined Significance [ASCUS] when co-existing with High Risk HPV than when only the viral infection is present.[34] As only 1% of HSIL cases seen in this study harbored the protozoan, it's unlikely that the organism has a significant role in its pathogenesis.[34]

Theileria spp

Theileria is a genus of parasitic protozoan that belongs to the phylum Apicomplexa and is closely related to Plasmodium. This intracellular protist is known to cause significant disease and death in both man and cattle, in Africa and Asia.[23] Theileria incites reversible transformation of leucocytes, and induces lymphoproliferative diseases, which is often lethal.[35]

Theileria is equally known to induce the inhibition of apoptosis. It effects its anti apoptotic effect via the activation of NF-kb sequestering [and thus inhibiting] the TP53 protein.[23,35,36] It equally enhances the secretion

of Granulocyte Monocyte-Colony Stimulating Factor [GM-CSF] which stimulates host cell proliferation. This cytokine [GM-CSF] induces the oncogene c-Myc, while constitutive activation of the oncogene C-jun kinase has also been documented.[37-39] Theileria spp has also been known to alter host cell cytoskeleton, increasing the motility of host cells, causing them to behave as leukocyte metastasis.[23]

Blastocystis hominis

Blastocystis Hominis is a protozoan intestinal parasite belonging to the Blastocystis genus of Stramenopiles-vast array of organisms including brown algae, water molds, and diatoms. It has a widespread geographic distribution and is found in countries of all income levels across the world.[40] This genus of single celled parasites is the most common protozoan infection in the United States. Infection rates vary from about 23% in the States to up to 100% in less developed nations.[41] It's a very common cause of GI symptoms in cancer patients and the immunosuppressed.[42] A study carried out in Malaysia observed that 21.08% of patients with colorectal cancer were positive for Blastocystis infection.[43]

Blastocystis sp has been demonstrated to facilitate the growth of colorectal cancer cells in-vitro.[43] This pro-mitotic impact is mediated through two modalities. Firstly, cells of a colorectal carcinoma express higher levels of Interleukins 6 and 8 in the presence of Blastocystis. Signalling induced by these cytokines lead to increased cell turnover and impaired apoptosis.[42] In the same vein, dysregulation of the p 53 gene and an impaired immune response [due to altered secretion and action of Interferon gamma], contribute to growth of colonic cancer cells.[43]

Plasmodium falciparum

Alongside Epstein Barr Virus infection, holoendemic malaria, caused by Plasmodium falciparum infection, has strong but unproven links to Burkitt lymphoma.[44] Recently, Cysteine rich interdomain region 1a[CIDR-1a], a microbial protein found on the surface of infected erythrocytes has been demonstrated to interact with B lymphocytes. This induces B lymphocyte proliferation, cytomegaly, and secretion of immunoglobulins.[45,46]. This molecule has also been documented to protect B cells from apoptosis.[45]

NEW ROLES FOR ESTABLISHED PARASITIC CARCINOGENS

Schistosoma haematobium

Its long standing links to the causation of Squamous cell carcinoma of the bladder notwithstanding, Schistosoma haematobium has recently been linked to cancers of the prostate and squamous cell carcinoma of the cervix.[47-50] Further insight into the oncogenic potential of this trematode has emerged, as a number of studies have uncovered key molecular events such as activation of the H-Ras oncogene and inactivation the tumour suppressors p53 and Retinoblastoma [Rb] genes have been observed in cases of Schistosomiasis associated with cancer of the bladder.[51,52,53]

Schistosoma mansoni and Schistosoma japonicum

Although Schistosoma haematobium appears to be the only member of this specie that has an established role in cancer formation. The documented link between infection by this trematode and squamous cell carcinoma of the bladder has affirmed its status as a carcinogen. Interestingly, new insights have merged on the relationship between other members of this specie and cancers. Fifty one [51%] of cases of Hepatocellular Carcinoma [HCC] seen in Japan, had infection with Schistosoma japonicum.[54] A post mortem study involving 571 autopsies demonstrated an increased incidence of Schistosomiasis among cases of HCC.[54] This malignancy appears early and in larger numbers in experimental S.jap infection.[55] In China, a case control analysis showed a strong association between Schistosoma japonicum infection and rectal carcinoma but no association with Colonic Carcinoma.[55]

There have been isolated case reports linking Schistosoma mansoni and cancer of the prostate, whereas the organism also has a direct association with HCC. A study of 1577 spleen biopsies from patients with Schistosoma mansoni infection showed the presence of follicular lymphomas.[6] Patients with Schistosoma japonicum have higher rates of infection with Hepatitis B and Hepatitis C viruses. This can be partly explained by the increased use of parenteral medication and blood transfusions. In addition cell mediated immunity in active Schistosoma japonicum, thus promoting chronic infection by these viruses.[55] Mostafa in Egypt, observed a direct relationship between chronic Schistosomiasis and Hepatocellular carcinoma, that wasn't restricted to its potentiating of viral hepatitis.[56]

Altered expression of the tumour suppressor protein p53 in cases of colorectal cancer associated with schistosomal colitis indicates that it is an early / inciting event in the development of colorectal cancer.[54,57] Schistosoma mansoni impairs the functions of cytochrome enzymes, cytoP450, cyto b-5 and NADPH cyto reductase activity, all leading to enhanced effects of aflatoxin on the liver.[6]

Opistorchis viverrini

Opistorchis viverrini, known to be a causative agent of bile duct cancer, has been demonstrated to secrete a

protein, Granulin[Ov-GRN-1], which is reported to be the only helminth induced growth factor known to induce proliferation of mammalian cells.[58, 59] Its human homologue, Human GRN is known to inhibit apoptosis, induce angiogenesis , tumour invasion and anchorage independence.[59,60]

Taenia solium

Neurocysticercosis is the most common parasitic infection of the central nervous system.[61] Caused by the tapeworm Taenia solium, it has been associated with gliomas of the central nervous system. The association between neurocysticercosis and gliomas has been mostly reported in endemic regions.[61, 62] A number of studies have demonstrated direct and indirect links between neurocyctcercosis and gliomas. It has been hypothesized that the chronic inflammation induced by the parasite may cause cellular proliferation and increases the risk of mutations. Conversely, some authorities have suggested that the neurocysticercosis was a consequence rather than a cause of the formation of gliomas.[61, 62] This disproved hypothesis was hinged on the suggestion that the immunosuppressed state induced by the cancer would promote the growth of cysticerci.[63,64]

CONCLUSION

With increased sensitivity and specificity of laboratory techniques and the consequent proficiency in demonstrating alteration of cell proliferation and apoptosis, the role of protozoa in cancer formation has been established. Inasmuch as this could partly explain the sustained increase in the number of malignancies seen in Sub Saharan Africa and other tropical regions of the world, it equally signals the need to screen for cancer associated parasites and treat/give prophylaxis.[7]

The multi-step nature of microbial/protozoan carcinogenesis provides ample opportunities for interventions to mitigate/prevent cancer.[65] Antimicrobial treatments have a favourable effect on prognosis in cancers and Oncologists will benefit from an understanding of the mechanisms of infected related carcinogenesis to develop novel effective cancer control strategies. In the same vein, a much more robust investment of resources should be made in the screening and treatment of chronic parasitic infection, as well as a heightened index of suspicion of incipient neoplastic transformation in a background of such infections.

Conflict(s) of interest:

The authors hereby declare that there are no conflicts of interest regarding the publication of this paper

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